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Data collection has been completed and manuscript preparation is in progress for all of the human studies outlined in this proposal. Findings to date include 1) lack of changes in attention and memory functions during pregnancy and lactation, 2) lack of difference in hormonal and anxiety responses to psychological stress, 3) enhanced lymphocyte proliferation and insensitivity to cytokine suppression by glucocorticoids in lactating women, and 4) increased blood pressure and heart rate and decreased vagal tone in postpartum, nonlactating women.

Data collection is in progress or complete for animal studies outlined in this proposal. Consistent with the human studies described above, enhanced lymphocyte proliferation has been found in lactating rats compared to nonlactating rats and virgins. These data from rats and humans identify a heretofore unrecognized benefit of lactation. We also have expanded our analysis of the "anti-stress" effects of the hormones of lactation to use a second rodent model, the prairie vole. We have discovered that prairie voles have responses to oxytocin which are similar to those reported in humans, and plan to continue to use this model to understand the mechanisms through which lactation influences mammalian responses to stress.

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FOREWORD

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CS Carter 10-12-97

PI - Signature Date

Lactation and Reactivity to Physical and Psychological Stress

Annual Report 1996-1997

TABLE OF CONTENTS

1. Introduction p. 5
2. Body p. 5-7
3. Conclusions p. 7
4. References p. 8
5. List of Personnel p. 9

INTRODUCTION

The purpose of this research project "Lactation and Reactivity to Physical and Psychological Stress" is to determine the effects of lactation on several different components of stress responses in both humans and animal models. Specific studies are in progress in humans to assess the effects of lactation on cognition, immune responses to inflammatory antigens, and hormonal, physiological and anxiety responses to psychological stress. In animals, parallel studies are in progress to measure immune responsivity, and behavioral, hormonal and physiological responses to physical and psychological stressors. In addition studies are planned in animals to attempt to identify the specific lactational hormones which generate the apparent reductions in behavioral and physiological responses and increased inflammatory responsivity during lactation.

BODY

Aim 1. Human Research: Cognitive performance

Recruitment, screening and cognitive testing of 20 control subjects, 20 pregnant subjects, 20 postpartum lactating subjects and 20 postpartum nonlactating subjects has been completed using both the selective attention and the implicit/explicit memory paradigms outlined in the original proposal. Data analysis was completed for the selective attention test and the implicit/explicit memory paradigm. The four groups of subjects did not differ on either test. Since group differences were not found we did not retest the lactating women after weaning. This work is being prepared for publication at present. These findings suggest that neither pregnancy nor lactation inhibits the capacity of women to perform cognitive tasks requiring selective attention or implicit/explicit memory. In our earlier work we had shown that lactating women were less reactive to the stress of exercise than recently delivered nonlactating (bottle-feeding women) (Altemus, et al., 1995).

This work has led Dr. Altemus to conduct an additional study of lactating women. This study is part of Dr. Altemus's own research program and was not outlined in the original grant proposal, but is described here because of its implications for understanding the effects of lactation of human responses to stress. In that study the response to acoustic startle was compared between twenty-five postpartum lactating women and 25 postpartum nonlactating women. Lactating women had enhanced eyeblink responses to acoustic startle, which we interpret as further evidence of reduced cognitive arousal and anxiety during lactation. This new finding parallels previous finding in our laboratory of reduced acoustic startle responses in patients with obsessive-compulsive disorder and increased responses after treatment with the antidepressant/antianxiety agent fluoxetine.

Aim 2. Human Research: Endocrine and immune effects of psychological stress

Recruitment, screening and testing of 15 control subjects, 23 lactating and 15 postpartum nonlactating women has been completed. Psychological stress testing was performed as described in the original proposal using the Trier Social Stress Test.

Data analysis has been completed for the endocrine and physiological data. In response to the stress interview, all three groups of subjects showed significant increases in anxiety, heart

rate, systolic and diastolic blood pressure, and ACTH and cortisol secretion. No difference were found in the hormonal (ACTH and cortisol) or anxiety responses to psychological stress among the three conditions. However, blood pressure and heart rate at baseline and during stress was significantly elevated in the postpartum, nonlactating women compared to controls and lactating women. In addition, vagal tone was reduced in postpartum nonlactating women compared to controls and lactating women. (Under other conditions higher levels of stress are correlated with reduced vagal tone.) This manuscript has been completed and submitted for publication.

Several changes in immune function were noted in post-partum women, both at baseline and in response to stress. Compared to control women, both lactating and nonlactating post-partum women had increased lymphocyte proliferation to a T-cell mitogen (PHA) at baseline and throughout the psychological stress test. In contrast, the baseline response to the B-cell mitogen (pokeweed) was reduced in both groups of post-partum women. In addition, post-partum women did not show the usual decrease in proliferation to either the B-cell or the T-cell mitogen during stress. In addition, post-partum, nonlactating women had elevated total white blood cell counts with a normal distribution of white cell subpopulations. Data analysis for this study has been completed and the manuscript will be submitted in the coming year. In a separate ex vivo study, lipopolysaccharide stimulated cytokine (IL-1 and IL-6) release was resistant to dexamethasone suppression in lactating women compared to controls. Estrogen and progesterone levels were similar in lactating women and controls, suggesting that lactational hormones such as oxytocin and prolactin may be responsible for these changes, rather than suppression of gonadal steroids. In addition, comparison of results from the same paradigm in women in the early follicular and midluteal phases of the menstrual cycle indicate that suppression of estrogen and progesterone in the early follicular phase is also associated with resistance to dexamethasone suppression. Thus lactating women may have resistance due to additive effects of both suppression of gonadal steroids and other lactational hormones. Cytokine assays and data analysis of samples from bottle-feeding women and pregnant women are in progress. We expect to submit these studies for publication in the coming year.

Taken together these study suggest that neither lactating nor pregnant women have obvious deficiencies in attention or memory. However, lactating women are less reactive to physical and psychological stressors than recently-delivered women who are not nursing their infants. These results support the hypothesis that lactation offers physical and mental health benefits to women (reviewed Carter and Altemus, 1997).

Aim 3. Animal Research: The behavioral effects of lactation

We found a reduction in conditioned freezing behavior and in the ACTH and corticosterone responses to conditioned freezing in lactating rats. We also have established the plus maze testing paradigm in our laboratory and found increased exploration of the open arms of the maze in lactating rats. Manuscripts describing these initial studies are in preparation.

Aim 4. Animal Research: Possible mechanisms for the behavioral and physiological effects of lactation.

Two behavioral paradigms to be used in these studies have been established in our laboratory as described above, and reliability testing with two additional paradigms, swim stress and open field, were completed. We did not find a difference in acoustic startle reactions in

lactating vs. nonlactating rats, so acoustic startle will not be used for dissection of the hormonal mechanisms underlying reduced stress responses and reduced fear behaviors in lactating rats. Instead we will use the conditioned freezing paradigm to model psychological stress or fear.

We also have discovered that another rodent model, the prairie vole, shows a response to the hormones of lactation that is similar to that previously reported in humans. In prairie voles, central injections of oxytocin immediately inhibit HPA axis activity resulting in a 50 percent decline in corticosterone levels. In contrast, in rats acute oxytocin treatments produce an increase in corticosterone levels. Because prairie voles, but not rats, show responses which parallel those of women, we plan to continue our analysis of the anti-stress effects of lactational hormones in voles.

CONCLUSIONS

1. Cognition, as measured by selective attention and implicit and explicit memory tasks is not affected by pregnancy or lactation.

2. Lactating women have enhanced eye blink responses to acoustic startle, consistent with a reduction in baseline arousal.

3. Lactation does not affect the anxiety, or endocrine responses to psychological stress. However, failure to lactate postpartum in associated with increases in heart rate and blood pressure and a reduction in vagal tone, compared to controls and lactating women.

4. Compared to control women, lactating women are resistant to glucocorticoid suppression of pro-inflammatory cytokines.

5. Compared to control women, both lactating and nonlactating postpartum women are resistant to stress-induced suppression of lymphocyte proliferation. Lymphocyte responses to T-cell mitogens is enhanced and response to B-cell mitogens is reduced in postpartum women.

6. Lactating rats show less fear behavior and less stress hormone responsivity in animal models of anxiety. Lactating rats do show reduced conditioned freezing responses and increased exploration in a novel environment. Lactation does not affect acoustic startle responses in rats.

7. Lactating rats have enhanced lymphocyte proliferation in response to T-cell mitogens.

8. Work with prairie voles shows that this rodent model exhibits hormonal responses that parallels findings in women. In both voles and humans oxytocin, a primary lactational hormone, inhibits the HPA axis. We propose to use this model to provide a more precise analysis of the anti-stress effects of lactation.

9. A better understanding of the physiological and behavioral consequences of lactation can be used to inform policy regarding the military deployment of women.

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PERSONNEL

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APPENDICES

None